REMARKS

Claims 1-24 were pending. Claims 25-43 were withdrawn by the Examiner as being drawn to a non-elected invention. Claims 1, 3, 11, and 18 are amended herein. Support for the amendment can be found throughout the specification, and thus it is believed that no new matter has been added. Claims 2 and 25-43 are canceled herein. Claims 1 and 3-24 are pending. No claim is allowed.

Formal Matters

Applicants gratefully acknowledge the entry of the Amendment, Petition to Correct Inventorship, and Declaration submitted Pursuant to 37 C.F.R. § 1.132 received by the Patent Office on May 15, 2003 as well as the acceptance of the amended title.

Applicants also appreciate the withdrawal of the rejections of record under 35 U.S.C. § 112, first and second paragraphs.

The abstract as amended in the Amendment and Response under 35 C.F.R. § 1.111 filed April 23, 2003 is presented herein on a separate page as requested by the Examiner and the priority information is updated herein.

Applicants hereby cancel claims 2 and 25-43.

The Office asserts that the references submitted are directed towards non-analogous art and suggest that Applicants are trying to "bury" relevant prior art references. Again, Applicants **strenuously object** to this gross mischaracterization of a routine practice in patent prosecution. First, these references include all of the references of the related parent cases. This is a common practice before the Office and, in fact, is required if the Applicant desires the printing of the considered references on the face of the patent. *See* MPEP § 609(I)(A)(2). Applicants desire the printing of all of the references from the parent applications also be printed on the face of the patent. Second, Applicants note that a number of the references relate to proteasomes, their biology, and various inhibitors and other relate to bone biology and growth. The nature of at least these

references as analogous art is self-evident from the titles and abstracts of the references. Third, the Examiner has now examined this very set of references in at least seven related cases, five of which have been allowed. Only in the most recent cases has the Examiner started asserting that Applicants have buried relevant prior art references. Finally, Applicants note that the Examiner has returned a signed IDS 1449 form indicating his full consideration of the submitted references. Applicants believe it is highly unlikely that the skilled artisan would characterize the references relating to bone biology and growth and proteasomal biology as non-analogous art. Indeed, the absence of references directed to the use of the claimed compounds to stimulate hair growth in the references submitted to date is a reflection of the novelty of the invention. Nonetheless, in an effort to expedite the prosecution of this application, the Applicants point out that at least the following references address bone growth directly: Beck et al;, Bellows et al.; Burgener et al.; Ducy et al.; Garrett et al.; Ghosh-Choudhery et al.; Gowan et al.; Harris et al.; Majeska, et al.; Mundy et al.; Murray et al.; Rickard et al.; Sampath et al.; Tencer et al.; Wang et al.; Wozney et al.; US Patent Nos.: 4,761,471, 5,280,040 and 6,083,690; and WO 90/11366, WO 92/03125, WO 95/24211, WO 96/38590, WO 97/15380, WO 98/17267, WO 98/25460, and WO 00/02548. At least the following references address proteasomal biology: Wojcik, et al.; Wozney et al., Vintitsky et al.; Sin et al.; Peters; Brochmann Murray et al.; Meng et al.; Jensen et al.; Hilt et al.; Groll et al.; Garrett et al.; Figueiredo-Pereira et al.; Eloffson et al.; Craiu et al.; Coux et al.; Baumeister et al.; Adams et al.; WO 95/25533; U.S. Patent Nos. 6,083,903, 5,780,454, and 5,580,854.

Rejections Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

Claims 1-24 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1, 5-7, and 19-23 of co-pending Application 09/421,545. According to the Examiner, the conflicting claims are not identical, but they are not patentably distinct from each other because the present claims include limitations directed to the isoprenoid pathway specifically but are directed to the same compounds as is the '545. Claims 1-24 were also provisionally rejected over claims 48-70 of the co-pending Application No. 09/558,973. According to the Examiner, the claims are not identical, but they are not patentably distinct from each other because the present claims include limitations directed to the isoprenoid pathway

specifically but are directed to the same compounds as is the '973. Applicants traverse this rejection.

Applicants file herewith a Terminal Disclaimer regarding U.S. Patent Application Serial Nos.: 09/421,545 and 09/558,973, and therefore this rejection is now moot.

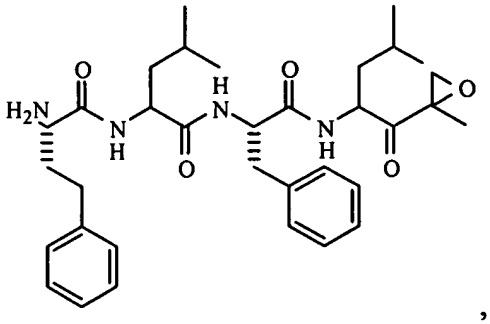
Therefore, Applicants respectfully request the withdrawal of this rejection.

Objection to the Specification

The Examiner objected to the specification as failing to provide proper antecedent basis for the claimed subject matter, citing 37 C.F.R. § 1.75(d)(1) and MPEP § 608.01(o), because the specification allegedly fails to provide written description for the presently claimed term "peptidyl aldehyde" in claim 18. The Examiner also objects to the specification as failing to comply with the sequence rules of 37 C.F.R. § 1.821-1.825. Applicants traverse these objections.

Applicants have amended the specification herein at page 28 to include the language of the original claim 18, which reads as follows:

18. The method of claim 3, wherein the compound is selected from the group consisting of



, epoxomicin, PS-341, NLVS, N-carbobenzoyl-Ile-Glu-(OtBu)-Ala-Leu-CHO (PSI) epoxide, lactacystin, PTX, and a peptidyl aldehyde

Applicants believe that this amendment provides the necessary antecedent basis for the term "peptidyl aldehyde."

Applicants submit herein sequence information to comply with the rules of 37 C.F.R. § 1.821-1.82.

In light of the above remarks, Applicants respectfully submit that the objections to the specification are overcome. Therefore, Applications request the withdrawal of the objections.

Rejections Under 35 U.S.C. § 102 (b)

Claims 1-3, 18, and 22-23 were rejected under 35 U.S.C. § 102 (b) as allegedly being anticipated by Tanihara (JP 6025288). According to the Examiner, Tanihara teaches the use of peptidyl aldehydes to treat osteoporosis in the English abstract. The Examiner also asserts that Tanihara teaches that fluoride may also be administered simultaneously as an anti-resorptive agent. The Examiner argues that all features of the claims are taught by the reference for the same function as claimed.

Claims 1-3, 18, and 22 were also rejected under 35 U.S.C. § 102 (b) as allegedly being anticipated by Murray. According to the Examiner, Murray teaches MG-132 or lactacystin treats and regulates osteoblasts related to chymotrypsin activity of the proteasome. The Examiner asserts that all features of the claims are taught by the reference for the same function as claimed.

Applicants traverse these rejections.

A. Tanihara fails to anticipate the claimed invention

Applicants respectfully submit that Tanihara fails to teach each and every element of the claimed invention and therefore does not anticipate the claimed methods. More specifically, Tanihara fails to teach the use of compounds that are proteasomal inhibitors to stimulate bone growth, and subsequently treat conditions such as osteoporosis. In fact, Tanihara is completely silent with regards to peptides, particularly peptidyl aldehydes, that are inhibitors of proteasomal activity. Tanihara discloses peptides with transforming growth factor (TGF)-β activity to treat various indications including osteoporosis. *See, e.g.*, Tanihara, at ¶1. Tanihara discloses the making and using of peptides with TGF-β activity that are less immunogenic than the native protein. It is well known in the art that TGF-β mediates its activities through the binding and activation of a cellular receptor, the TGF-β receptor, to initiate an intracellular signaling cascade. *See, e.g.*, Howe, P.H. *Transforming Growth Factor* β IN THE CYTOKINE HANDBOOK 1119, 1121 (4th Ed. 2003) (stating that the "cellular actions of TGF-β are mediated through binding to ... cell surface receptors"). Therefore, Tanihara discloses synthetic peptides that emulate TGF-β in

biological activity, presumably through binding to the TGF-β receptor. Applicants are unaware of any scientific evidence that TGF-β functions as a proteasomal inhibitor, and neither the Examiner nor Tanihara provide such evidence. Furthermore, contrary to the express assertion of the Examiner, this is no disclosure whatsoever regarding the simultaneous administration of fluoride as an anti-resorptive agent. The only mention of fluoride is in a description of the solid phase synthesis of the peptide with TGF-β activity while there is no mention of anti-resorptive agents at all. In view of the complete absence of any disclosure regarding the use of peptidyl aldehydes that are proteasomal inhibitors to stimulate bone growth, Tanihara fails to anticipate the claimed methods.

B. Murray is not a proper reference under 35 U.S.C. § 102(b)

Applicants submit that Murray is not a prior art reference relative to the instant application because the filing date of the relevant disclosure in the instant application pre-dates the publication date of Murray. The instant invention claims priority as a continuation in part to U.S. Application Serial No. 09/421,545, filed October 20, 1999, a continuation-in-part to U.S. Application Serial No. 09/361,775, filed July 27, 1999 (now 6,410,512), which is a continuation-in-part of U.S. Application Serial No. 09/113,647, filed July 10, 1998 (now U.S. Patent 6,462,019). MG-132, the compound disclosed in Murray, has a priority claim to the July 10, 1998 filing date of U.S. Patent 6,462,019. MG-132 is disclosed as a proteasomal inhibitor that stimulates bone growth in Example 2 (*e.g.*, column 17, lines 50-54) and Figure 1A. Also, the use of MG-132 to stimulate bone formation is specifically claimed in the original claim set of this application. *See, e.g.,* claims 3, 6, 9, and 14. Because the Murray reference has a publication date of August 1998, it post-dates the priority date of the claimed invention, and therefore it is not a proper reference under any subsection of 35 U.S.C. § 102. As a result, claim 19 is free from prior art.

In view of the above, Applicants respectfully submit that the basis for this rejection may be removed.

Rejection Under 35 U.S.C. § 103 (a)

Claims 1-24 were rejected under 35 U.S.C. § 103 (a) are allegedly being unpatentable over the combination of Murray in view of each of Spaltenstein, Adams (Bioorg Med Chem Lett),

and Adams (US 6,083,903 and US 6,297,217). According to the Examiner, Murray teaches MG-132 or lactacystin treats and regulates osteoblasts related to chymotrypsin activity of the proteasome. The Examiner asserts that the claims differ from Murray in that some of the claims read on additional compounds for treating bone. According to the Examiner, Spaltenstein teaches Ile-Ile-Phe-epoxyketones and other analogs, thus reading on L-isoleucinamide. The Examiner asserts that Adams (Bioorg Med Chem Lett) teaches selective dipeptidyl boronic acid proteasome inhibitors, discloses the inhibition of chymotryptic activity of the proteasome complex, and discloses compounds that read on L-isoleucinamide. Adams (US 6,083,903 and US 6,297,217) allegedly teaches compounds that are proteasomal inhibitors. Therefore, the Examiner argues that it would have obvious to one of skill in the art to employ the compounds of Spaltenstein and Adams in the method of Murray because Murray discloses inhibiting chymotrypsin activity of the proteasome to enhance bone formation and to then employ any compound that is known to inhibit chymotrypsin activity of the proteasome to treat bone. Applicants traverse this rejection.

As discussed above, Murray is not a proper reference under 35 U.S.C. § 102 (b), and therefore is not available as a § 103 (a) reference. The combination of Spaltenstein, Adams, and Adams fails to result in the claimed methods, and therefore does not render the claimed methods obvious. None of these references contains any disclosure whatsoever regarding the use of the disclosed compounds to stimulate bone formation. More specifically, Spaltenstein is silent with the use of the disclosed compounds to stimulate bone growth. All of the Adams references disclose the use of the disclosed compounds in the treatment of diseases such as cancer and inflammation. In fact, Adams largely seems to be relying on an anti-proliferative effect of its compounds to treat the disclosed disease states. *See, e.g.*, U.S. 6,297,217 at col. 28, line 13-16. The only disclosure related to bone disease is a suggestion that the compounds can be use to treat inflammation associated with osteoporosis. *See, e.g.*, U.S. 6,297,217 at col. 27, lines 19-25. Thus, the combined teachings of these references fail to teach or suggest the use of the disclosed compounds to stimulate bone growth, failing to render the claimed methods *prima facie* obvious.

In view of the above, Applicants respectfully submit that the basis for this rejection may be removed.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding objections and rejections of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 432722002623. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: June 29, 2004

Respectfully submitted,

By _____

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